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(54) Macrolide compositions for treating gastro-intestinal motility disorders.

(57) Pharmaceutical compositions comprising as an active ingredient a ring-contracted macrolide. The macrolides, some of which are novel compounds, enhance gastrointestinal motility. Methods for treating gastrointestinal motility disorders with these macrolides and processes for their preparation are also provided.

EP 0 349 100 A2

MACROLIDE COMPOSITIONS

This invention provides novel pharmaceutical compositions which comprise as an active ingredient a 12-membered macrolide compound. These compositions ar especially useful for treating gastrointestinal motility disorders in animals. Novel compounds and methods for testing gastrointestinal motility disorders are also disclosed.

The gastrointestinal tract transports ingested food material from oral to aboral direction in a well coordinated fashion. Transport is brought about by peristaltic contractions of the circular muscle layers. Coordination of the transport is accomplished by integrated central and peripheral nervous inputs.

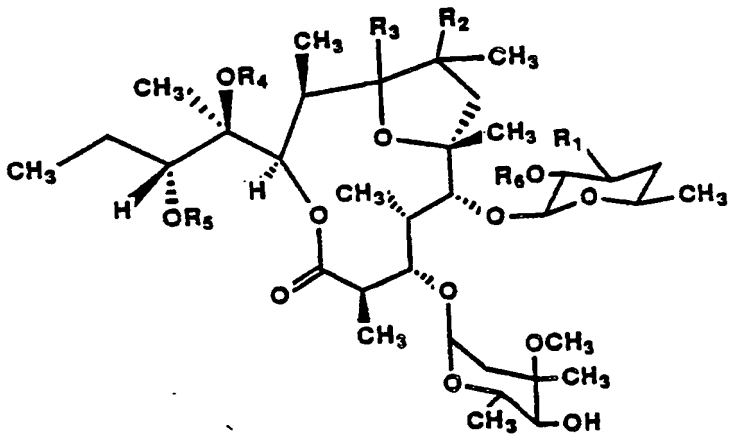
Defects in the normal motility pattern can lead to development of aperistalsis, enhanced transit, gastrointestinal stasis (such as that seen in diabetic gastroparesis) or to an adynamic ileus. One prevalent defect, when lower esophageal sphincter tone is low, causes retrograde propulsion of stomach contents into the esophagus. This problem can lead to the development of esophagitis.

The exact pathophysiology of motility disorders is not well understood. Consequently, a rational therapy for treating these disorders is also not available. Pharmacological agents which enhance the motility in the paralytic gut may have usefulness in the treatment of diseases such as dyspepsia, gastroparesis, gastroesophageal reflux disease and surgery-induced adynamic ileus. Additionally, motility-enhancing agents (also called gastroprokinetic agents) may facilitate the placement of diagnostic instrumentation in the gastrointestinal tract.

Currently, metoclopramide, a benzamide with dopamine D2-receptor antagonist activity, is the only drug approved in the United States for treating motility disorders. Unfortunately, metoclopramide has several side effects, which range from prolactin increase to development of dyskinesia, etc. Thus, the need for a potent, selective, efficacious and safe drug to treat gastrointestinal motility disorders is great.

Since the introduction of macrolide antibiotics clinically, it is known that they can cause abdominal cramps and diarrhea. Whether these side effects are secondary to their antibiotic activity or are due to their effect on gastrointestinal motility and secretion is not known. Recently, Omura et al. chemically modified erythromycin in an attempt to find compounds with improved gastroprokinetic properties, but with negligible antibacterial activity (See J. Med. Chem. 30(11):1941-1943, 1987; J. Antibiotics 38(11):1631-1632, 1987; Ther. in 21st Cent. Jap. U.S. Cong. Pharm. Sci. abstract #14, 1987; Interscience Conf. Antimicrob. Agents & Chemotherapy, abstract #1149, 1985). Omura's group reported that several of the compounds they prepared showed gastroprokinetic potency greater than that of erythromycin. The in vitro activity of the most potent of these compounds, however, was not inhibited by nerve blocking agents (tetrodotoxin, TTX) or by a cholinergic muscarinic antagonist (atropine).

In this invention there is provided new pharmaceutical compositions which comprise as an active ingredient a ring-contracted macrolide of formula (I):



(I)

wherein

R_1 is $-N(CH_3)_2$ or $-[N(CH_3)$ [redacted] X^-;
R is C_1-C_6-alkyl, C_2-C_6-alkenyl,
C_2-C_6-alkynyl, benzyl or benzyl substituted by from 1 to 3 substituents selected from fluoro, chloro, C_1-C_4-alkyl, C_1-C_4-alkoxy, nitro, C_1-C_4-alkoxycarbonyl, $-N(C_1$-C_4-alkyl$)_2$ or cyano;
R_2 and R_3 each ar H or together form a bond;
R_4 and R_5 independently are H or C_1-C_4-acyl,
or together with a carbonyl group form a five-membered cyclic carbonate;
R^6 is H or C_1-C_4-acyl; and
X^- = halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, C_1-C_3-alkylsulfonate or arylsulfonate (such as p-toluenesulfonate or benzenesulfonate);
or, when R_1 = $-N(CH_3)_2$, a pharmaceutically acceptable salt thereof;
for use in the treatment of gastrointestinal motility disorders.

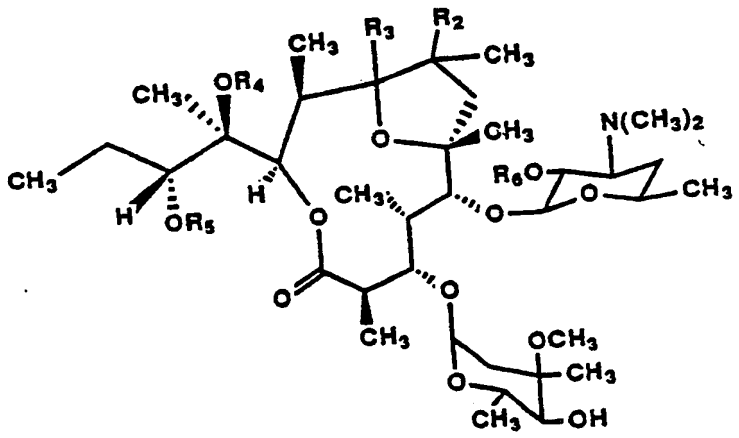
The formula (I) compounds are both chemically and biologically different from those reported by Omura et al. The formula (I) compounds enhance gastrointestinal motility through the cholinergic mechanisms which are primarily utilized by the normal gut. This mechanism of action is demonstrated by the fact that the gastrointestinal motility enhanced by the formula (I) compounds was blocked by atropine (30 µg/kg). In addition, these potent gastroprokinetic macrolides have the desirable feature of having minimal antibiotic activity.

Thus, this invention provides a compound of formula (I) for use in the treatment of gastrointestinal motility disorders.

In a further aspect, this invention provides a group of novel compounds, i.e. the compounds of formula (1) wherein R_1 = $-[N(CH_3)_2R]^+X^-$.

This invention also provides a process for preparing a macrolide of formula (I) wherein R_1 is $-[N(CH_3)_2R^+]X^-$, which comprises:

(A) (i) reacting a macrolide of formula (II)



(II)

with an alkylating agent so as to prepare a formula (I) compound wherein R_1 is $-[N(CH_3)_2R]^+X^-$;
and, optionally,
ii) reducing the Step (A)(i) compound so as to prepare a formula (I) compound wherein R_1 is $-[N(CH_3)_2R]^+X^-$ and R_2 and R_3 each are H;
or

(B)(i) reducing a macrolide of formula (II) so as to prepare a formula (1) compound where R_1 is $-N(CH_3)_2$ and R_2 and R_3 each are H;
and/or optionally salifying the compound, if not in salt form; and,
optionally,
ii) reacting the Step(B)(i) compound with an alkylating agent so as to prepare a formula (I) compound wherein R_1 is $-[N(CH_3)_2R]^+X^-$ and R_2 and R_3 each are H.

As used herein, the term "alkyl" includes straight, branched and cyclic hydrocarbon moieties and

combinations thereof containing the specified number of carbon atoms.

The terms "alkenyl" and "alkynyl" refer to those alkyl groups which contain from 1 to 2 double and/or triple bonds. The double bonds can be in either the cis or trans configuration.

The term "C_1-C_4-acyl" refers to an acyl moiety derived from a carboxylic acid containing from one to four carbon atoms.

The term "halide" means chloride, bromide or iodide.

The term "carboxylate" refers to the anion of an organic carboxylic acid such as acetic, succinic, citric, lactic, maleic, fumaric, palmitic, cholic, pamoic, mucic, D-glutamic, d-camphoric, glutaric, glycolic, phthalic, tartaric, formic, lauric, stearic, salicylic, methanesulfonic, benzenesulfonic, sorbic, picric, benzoic, cinnamic, and like acids.

Certain derivatives of this invention form salts, particularly acid addition salts. These acid addition salts are also useful as gastroprokinetic agents and are a part of this invention. In another aspect, such salts are useful as intermediates, for example, for separating and purifying the derivatives. In addition, the salts have an improved solubility in water.

Representative suitable salts include those salts formed by standard reactions with both organic and inorganic acids such as, for example, sulfuric, hydrochloric, phosphoric and the organic acids listed supra.

Pharmaceutically acceptable acid addition salts are an especially preferred group of salts of this invention. Pharmaceutically acceptable acid addition salts are those salts useful in the chemotherapy of a warm-blooded animal.

Typical formula (I) compounds are shown in Table I.

Table I

Illustrative Formula (I) Compounds

Compound Number	R_1	R_2	R_3	R_4	R_5	X[c]
1	$-N(CH_3)_2$	--db[a]--		H	H	----
2	$-N(CH_3)_2$	--db--		--C(=O)-[b]--		----
3	$-N(CH_3)_2$	H	H	H	H	----
4	$-N(CH_3)_2$	H	H	--C(=O)--		----
5	$-N(CH_3)_3^+$	--db--		H	H	I
6	$-N(CH_3)_2(CH_2C{\equiv}CH)^+$	--db--		H	H	Br
7	$-N(CH_3)_2(CH_2CH=CH_2)^+$	--db--		H	H	Br
8	$-N(CH_3)_2[CH_2C(CH_3)=CH_2]^+$	--db--		H	H	Cl
9	$-N(CH_3)_2[(CH_2)_3CH_3]^+$	--db--		H	H	Br
10	$-N(CH_3)_3^+$	H	H	H	H	I
11	$-N(CH_3)_3^+$	H	H	--C(=O)--		I
12	$-N(CH_3)_3^+$	--db--		--C(=O)--		$\frac{1}{2}SO_4$
13	$-N(CH_3)_2(CH_2C{\equiv}CCH_3)^+$	--db--		H	H	OTs
14	$-N(CH_3)_2(CH_2C{\equiv}CH)^+$	H	H	H	H	OMs
15	$-N(CH_3)_2(CH_2C{\equiv}CH)^+$	--db--		Ac	Ac	OAc
16	$-N(CH_3)_2CH_2Ph^+$	--db--		H	H	Br

[a] R_2 and R_3 together form a bond

[b] R_4 and R_5 together with a carbonyl group form a 5-membered cyclic carbonate

[c] Ts = tosylate; Ms = mesylate; and Ac = acetate

Pharmaceutical compositions which comprise as an active ingredient a formula (I) compound and one or more pharmaceutically acceptable carriers therefor are also part of this invention. These pharmaceutical

compositions can be formed for oral or parenteral administration for therapeutic or prophylactic treatment of gastrointestinal motility disorders.

For example, a formula (I) compound can be admixed with conventional pharmaceutical carriers and excipients and used in the form of tablets, capsules, elixirs, suspensions, syrups, wafers and the like. The compositions comprising a compound of this invention will contain from about 0.1 to about 90% by weight of the active compound, and more generally from about 10 to about 30%.

The compositions may contain common carriers and excipients, such as corn starch or gelatin, lactose, sucrose, microcrystalline cellulose, kaolin, mannitol, dicalcium phosphate, sodium chloride and alginic acid. Disintegrators commonly used in the formulations of this invention include croscarmellose sodium, microcrystalline cellulose, corn starch, sodium starch glycolate and alginic acid.

Tablet binders that can be included are acacia, methylcellulose, sodium carboxymethylcellulose, polyvinylpyrrolidone (Povidone), hydroxypropyl methylcellulose, sucrose, starch and ethylcellulose. Lubricants that can be used include magnesium stearate or other metallic stearates, stearic acid, silicone fluid, talc, waxes, oils and colloidal silica.

Flavoring agents such as peppermint, oil of wintergreen, cherry flavoring or the like can also be used.

It may be desirable to add a coloring agent to make the dosage form more esthetic in appearance or to help identify the product.

For intravenous (IV) use, a water soluble form of the compound can be dissolved in one of the commonly used intravenous fluids and administered by infusion. Such fluids as, for example, physiological saline, Ringer's solution or 5% dextrose solution can be used.

For intramuscular preparations, a sterile formulation of a suitable soluble salt form of the compound, for example the hydrochloride salt, can be dissolved and administered in a pharmaceutical diluent such as Water-for-Injection, physiological saline or 5% glucose. A suitable insoluble form of the compound may be prepared and administered as a suspension in an aqueous base or a pharmaceutically acceptable oil base, e.g. an ester of a long chain fatty acid such as ethyl oleate.

For oral use, solid formulations such as tablets and capsules are particularly useful. Sustained release or enterically coated preparations may also be devised. For pediatric and geriatric applications, suspensions, syrups and chewable tablets are especially suitable.

Alternatively, the unit dosage form of the compound can be a solution of the compound in a suitable diluent in sterile, hermetically sealed ampoules. The concentration of the compound in the unit dosage may vary, e.g. from about 1 percent to about 50 percent, depending on the compound used and its solubility and the dose desired by the physician.

In a further aspect, this invention provides a method for treating gastrointestinal motility disorders in animals. The term "treating" is used to denote both prevention of the disorder and control of the disorder after the host animal has become afflicted. The method comprises administering to the animal an effective dose of a compound of this invention. An effective dose is generally between about 0.02 and about 100 mg/kg of the compound or its pharmaceutically acceptable salt. A preferred dose is from about 0.05 to about 50 mg/kg of compound. A typical daily dose for an adult human is from about 50 mg to about 0.5 g.

In practicing this method, the compound compound can be administered as a single daily dose or in multiple doses per day. The treatment regime may require administration over extended periods of time, e.g., for several days or for several weeks. The amount per administered dose or the total amount administered will depend on such factors as the nature and severity of the problem and the age and general health of the patient. A convenient method of practicing the treatment method is to administer the compound orally, using tablets, capsules, suspensions, syrups and the like. The compound may also be administered by other methods, e.g. as a suppository or parenterally via IV infusion.

We provide the following non-limiting examples in order to illustrate this invention.

Product purification by chromatography was performed on silica gel, using either flash chromatography techniques (E. Merck grade 60 silica gel, 230-400 mesh) or a Waters Model 500 Prep LC system.

Compounds were purified to homogeneity according to thin layer chromatographic (TLC) and proton NMR analyses.

Preparation 1

8,9-Anhydro-erythromycin-6,9-hemiketal

A solution of erythromycin (20.0 g, 27.3 mmol) in glacial acetic acid (100 ml) was stirred at room temperature for 1 hour. Sodium hydroxide (5N) was slowly added in portions. After each addition, the mixture was allowed to return to ambient temperature. After precipitation was complete, the mixture was extracted twice with dichloromethane. The combined organic layers were extracted with saturated sodium bicarbonate solution, dried (sodium sulfate), filtered and evaporated. The crude produce (18.9 g) was purified by preparative HPLC (linear gradient of dichloromethane to 7% methanol + 0.5% ammonium hydroxide in dichloromethane) to yield the title compound (13.2 g, 68%) as a white solid.

EXAMPLE 1

Preparation of Compound 1

8,9-Anhydro-erythromycin-6,9-hemiketal (10.0 g, 14 mmol) in methanol (200 mL) was treated with potassium carbonate (1.9 g, 14 mmol), and the mixture was refluxed for 90 min. Solvent was evaporated under reduced pressure, and the residue was partitioned between dichloromethane and saturated sodium bicarbonate solution. The organic layer was evaporated to give 9.6 g of a white foam. This foam was purified by preparative HPLC (linear gradient of dichloromethane to 7.5% methanol + 0.5% ammonium hydroxide in dichloromethane) to yield Compound 1 (5.4 g, 54%) as a white solid. FDMS m/e 715 (M + H).

EXAMPLE 2

Activity of the Formula (I) Compounds

Motility in the stomach and duodenum was recorded using standard techniques (P. Bass and J.N. Wiley, Am. J. Physiol. 208:908-913, 1965). Briefly, ferrets of either sex, weighing 1.0-1.5 kg were anesthetized by pentobarbital (30 mg/kg, i.p.). Anesthesia was maintained by injecting pentobarbital as a bolus dose (5 mg/kg, i.v.) as required. All animals were allowed to breath spontaneously through a tracheal tube. The jugular artery and vein were cannulated to record blood pressure and inject test substances. Body temperature was maintained using a heated water jacket. An abdominal incision was made to expose the stomach and proximal duodenum. Strain gauges (R. B. Products, Wisconsin) were sewn on the serosal surface of the stomach and duodenum 2 cm proximal and 2 cm distal to the pyloric sphincter, respectively. The strain gauges were oriented to record the force development in the circular muscle layer only, because the contractile activity of this muscle layer results in the propulsion of ingested food material. The abdominal cavity was closed with a towel clamp, and the output of strain gauge was displayed on a dynograph strip chart recorder.

The drugs were dissolved in 50% DMSO and were made fresh every day. The bolus injection was given rapidly and the i.v. line was flushed following the drug injection with 1/2 cc of physiological saline. A minimum 5-min. period was allowed between doses. However, if motility did not return to the pretreatment level, more time was allowed, but the time did not exceed 10 minutes. At the end of the experiment the animals were euthanized with a bolus dose of T-61 (1 cc).

The number and amplitude of contractions in the one-min. period following the bolus injection were manually calculated. The amplitude of all responses was averaged and is reported as grams of tension developed/minute. No statistical analysis was performed. Most of the compounds were tested at a screening dose of 10 µg/kg. However, a dose-response curve for the lead compound was determined.

Table II shows the effect of illustrative formula (I) compounds on the tension developed in the circular muscle layers of the stomach:

Table II

Effect of Formula (I) Compounds on Gastrointestinal Motility		
Compound[a]	Dose (IV, µg/kg)	Tension Developed (g/min.)
Erythromycin	100	1.40
1	7	1.40
1	10	2.15
1	30	3.45
2	20	2.95
5	10	6.97
6	20	1.80

[a]Compound numbers from Table I

EXAMPLE 3

An illustrative pharmaceutical tablet composition containing a formula (I) compound is made up as follows:

Ingredient	Parts by Weight
Compound 1	250
Polyvinylpyrrolidone	35
Microcrystalline cellulose	35
Sodium hydroxide U.S.P.	0.36
Potassium phosphate	1.32

Blend ingredients and granulate with 0.1 parts of water. Dry granules, pass through a 12-mesh screen and combine with the following:

Ingredient	Parts by Weight
Compound 1 granules	320
Sodium citrate dihydrate	300
Magnesium stearate	5

blend and tablet.

EXAMPLE 4

An illustrative intravenous composition containing a formula (I) compound is prepared by dissolving compound 6 in dilute (50%) dimethyl sulfoxide.

EXAMPLE 5

Preparation of Compound 2

A solution of erythromycin enol ether (500 mg, 0.7 mmol) and ethylene carbonate (1.0 g, 11.4 mmol) in 1,2-dimethoxyethane (25 mL) was treated with K_2CO_3 (500 mg, 3.6 mmol). The resulting mixture was heated to reflux with the exclusion of moisture. After 19 hours, an additional portion of ethylene carbonate (500 mg, 5.7 mmol) was added to the reaction, and heating was continued for 7 hours. The mixture was diluted with CH_2Cl_2 (50 mL) and extracted with H_2O (3 x 100 mL). The CH_2Cl_2 solution was dried (Na_2SO_4) and evaporated to dryness. The residue was chromatographed on a silica-gel flash column, using a 1-L gradient of CH_2Cl_2 to CH_2Cl_2/MeOH/NH_4OH (92.5:7.5:0.5), followed by 1L of the latter solvent, to give two products. The higher R_f product, 92 mg, was identical to the carbonate of erythromycin enol ether.

The second product was compound 2; yield: 215 mg.

IR($CHCl_3$): 1796, 1727 cm^{-1}

^1H NMR($CDCl_3$): δ 5.19 (d, H-11), 4.16 (dd, H-13 overlapped with H-3), 1.58 and 1.56 (2s, 8-Me and 12-Me)

FDMS: m/e = 741 (M+)

EXAMPLE 6

Preparation of Compound 6

To Compound 1 (1.0 g, 1.4 mmoles) in chloroform (20 mL), was added 12.6 mL of 80% propargyl bromide (in toluene). The mixture was stirred at 25° for 3 hours, and the solvent was removed in vacuo. The residue was dissolved in chloroform (5 mL). Diethyl ether was added until precipitation appeared to be complete. The solid was removed by filtration and recrystallized twice (chloroform/ether). The product was dried at 25° for 18 hours to give 827 mg (70.8 %) of compound 6 as an off-white powder.

Elemental analysis [experimental (theory)]: C: 56.79 (57.55); H: 8.02 (8.21); N: 1.72 (1.68); Br: 9.39 (9.57).

FDMS: m/z^+ 754 (M-Br), 715 (M-propargyl bromide).

^1H NMR (300 MHz): $N(CH_3)_2$ shift from δ 2.26 to δ 3.49 (6 protons).

EXAMPLE 7

Preparation of Compound 5

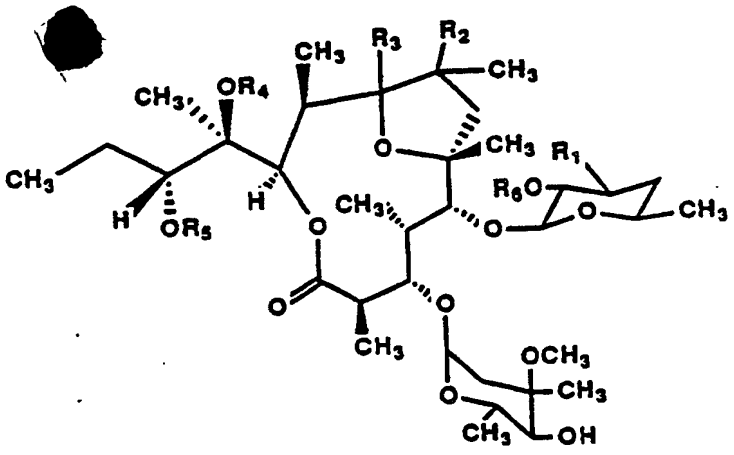
Compound 5 was prepared in an analogous manner to the preparation of Compound 6, starting with compound 1 (200 mg) and methyl iodide (80 µL) in chloroform (2 mL). Two recrystallizations gave 85 mg (35.4%) of the product as a tan solid.

FDMS: m/z^+ 730(M-1), 715 (M-CH_3I)

^1H NMR(300 MHz): $N(CH_3)_3$ δ 3.50 (9 protons).

Claims

1. A pharmaceutical composition which comprises as an active ingredient a compound of formula (I):



(I)

wherein
R_1 is $-N(CH_3)_2$ or $-[N(CH_3)_2R]^+X^-$;
R is C_1-C_6-alkyl, C_2-C_6-alkenyl,
C_2-C_6-alkynyl, benzyl or benzyl substituted by from 1 to 3 substituents selected from fluoro, chloro, C_1-C_4-alkyl, C_1-C_4-alkoxy, nitro, C_1-C_4-alkoxycarbonyl, $-N(C_1$-C_4-alkyl$)_2$ or cyano;
R_2 and R_3 each are H or together form a bond;
R_4 and R_5 independently are H or C_1-C_4-acyl,
or together with a carbonyl group form a five-membered cyclic carbonate;
R^6 is H or C_1-C_4-acyl; and
X^- = halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, C_1-C_3-alkylsulfonate or arylsulfonate;
or, when R_1 = $-N(CH_3)_2$, a pharmaceutically acceptable salt thereof;
and one or more pharmaceutically acceptable carriers therefor.

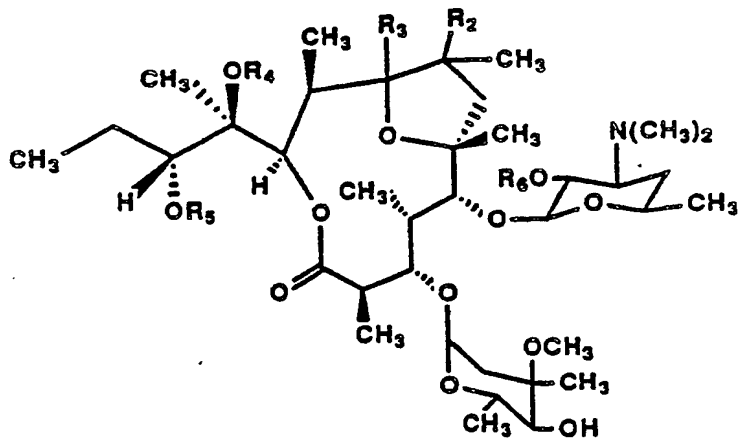
2. A composition as claimed in Claim 1 wherein the compound is one wherein R_1 is $-N(CH_3)_2$, R_2 and R_3 together form a bond and R_4, R_5 and R_6 are H.

3. A compound of formula (I) as defined in claim 1 or 2, for use in the treatment of gastrointestinal motility disorders.

4. A compound of formula (I) as defined in Claim 1 or 2 wherein R_1 is $-[N(CH_3)_2R]^+X^-$.

5. A compound of formula (I) as claimed in Claim 4 wherein R is C_1-C_6-alkyl. R_2 and R_3 together form a bond and R_4, R_5 and R_6 are H.

6. A process for preparing a compound of formula (I) as claimed in claim 4 or 5 which comprises:
(A)(i) reacting a macrolide of formula (II)

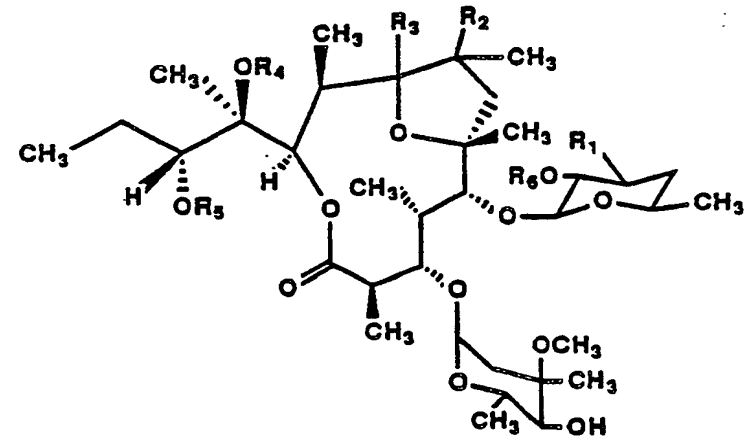


(II)

with an alkylating agent so as to prepare a formula (I) compound wherein R_1 is $-[N(CH_3)_2R]^+X^-$;
and, optionally,
ii) reducing the Step (A)(i) compound so as to prepare a formula (I) compound wherein R_1 is $-[N(CH_3)_2R]-\overset{\leftarrow}{X}^-$ and R_2 and R_3 each are H;
or
(B)(i) reducing a macrolide of formula (II) so as to prepare a formula (I) compound where R_1 is $-N(CH_3)_2$ and R_2 and R_3 each are H;
and/or optionally salifying the compound, if not in salt form;
and, optionally,
ii) reacting the Step(B)(i) compound with an alkylating agent so as to prepare a formula (I) compound wherein R_1 is $-[N(CH_3)_2R]^+X^-$ and R_2 and R_3 each are H.

Claims for the following Contracting States : GR, ES

1. A process for preparing a pharmaceutical composition which comprises admixing a compound of formula (I):



(I)

wherein
R_1 is $-N(CH_3)_2$ or $-[N(CH_3)_2R]^+X^-$;

R is C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, benzyl or benzyl substituted by from 1 to 3 substituents selected from fluoro, chloro, C_1-C_4-alkyl, C_1-C_4-alkoxy, nitro, C_1-C_4-alkoxycarbonyl, $-N(C_1$-C_4-alkyl$)_2$ or cyano;

R_2 and R_3 each are H or together form a bond;

R_4 and R_5 independently are H or C_1-C_4-acyl,
or together with a carbonyl group form a five-membered cyclic carbonate;

R^6 is H or C_1-C_4-acyl; and

X^- = halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, C_1-C_3-alkylsulfonate or arylsulfonate;

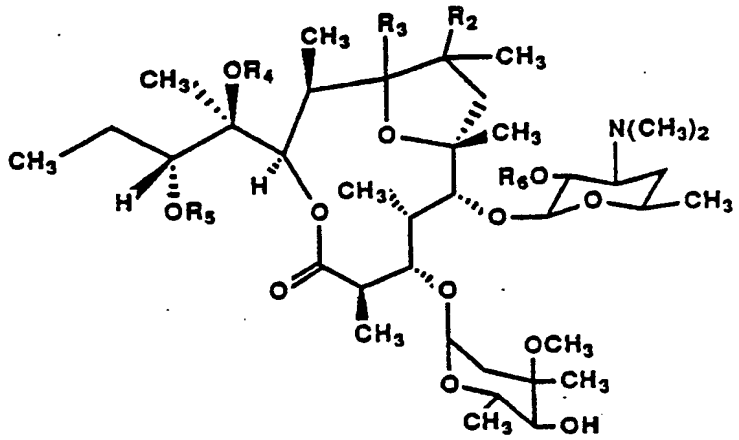
or, when R_1 = $-N(CH_3)_2$, a pharmaceutically acceptable salt thereof;

with one or more pharmaceutically acceptable carriers therefor.

2. A process as claimed in Claim 1 wherein the compound is one wherein R_1 is $-N(CH_3)_2$, R_2 and R_3 together form a bond and R_4, R_5 and R_6 are H.

3. A process for preparing a compound of formula (I) as defined in Claim 1 wherein R_1 is $-[N(CH_3)_2R]^+X^-$, which comprises:

(A)(i) reacting a macrolide of formula (II)



(II)

with an alkylating agent so as to prepare a formula (I) compound wherein R_1 is $-[N(CH_3)_2R]^+X^-$;
and, optionally,
ii) reducing the Step (A)(i) compound so as to prepare a formula (I) compound wherein R_1 is $-[N(CH_3)_2R]^+X^-$ and R_2 and R_3 each are H;

or

(B)(i) reducing a macrolide of formula (II) so as to prepare a formula (I) compound where R_1 is $-N(CH_3)_2$ and R_2 and R_3 each are H;
and/or optionally salifying the compound, if not in salt form;
and, optionally,
(ii) reacting the Step (B)(i) compound with an alkylating agent so as to prepare a formula (I) compound wherein R_1 is $-[N(CH_3)_2R]^+X^-$ and R_2 and R_3 each are H.